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Overlooking the transition elephant in the ultra-high-risk room: are we missing functional equivalents of transition to psychosis?

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Abstract

In the wake of the almost quarter of a century since the conceptualization of ultra-high-risk (UHR) states for psychosis, empirical evidences in the field are constantly scrutinized and re-assessed through meta-analytic lens. Briefly, such scrutiny converges on three major evidences: pretest risk enrichment, risk hierarchy within UHR states, and declining transition rates. While the former two are intuitive, the dilution effect remains elusive and might be rather symptomatic of unsolved issues in the field. Those include the heterogeneously reported antipsychotic (AP) exposure in UHR samples and the almost univocal focus on purely psychometric transition to psychosis. Both issues lead to the neglect of functional equivalents of transition, i.e. that of a mental state at immediate need for AP medication, and might have a cascading confounding effect on the predictive value of contemporary risk calculators centered on criterial transition as a unique outcome.

Partly amplifying previous observations by Ajnakina, David, and Murray (2018), Moritz, Gaweda, Heinz, and Gallinat (2019) systematically press central trigger points in contemporary early detection conceptual landscape. They highlight four reasons, including decreasing transition rates, why early detection centers for psychosis should be renamed and their treatment targets reconsidered. Transition to psychosis could be a more faceted outcome than usually thought and it is crucial to discuss potential limits of the concept itself and how these limits may have influenced the judgment on the early detection paradigm. Indeed, in the wake of the almost quarter of a century since the conceptualization of ultra-high-risk (UHR) states for psychosis (Yung & McGorry, 1996), empirical evidences are constantly re-assessed through meta-analytic lens, which converge on three key-points: (1) pre-test risk enrichment (Fusar-Poli et al., 2016a), (2) stratification of risk among UHR subgroups (Fusar-Poli et al., 2016b), and (3) progressive decline of transition rates to psychosis, aka 'dilution effect' (Fusar-Poli et al., 2016b; Hartmann et al., 2016; Simon, Umbricht, Lang, & Borgwardt, 2014; Yung et al., 2007).

The dilution effect and the Janus-faced nature of transition

Whereas pre-test risk enrichment and within-UHR gradient are rather intuitive phenomena, the dilution effect remains rather obscure in its genesis and multi-causality. Several concurrent and non-mutually exclusive factors have been hypothesized: the decrease of duration of symptoms prior to first clinical contact (Yung et al., 2007), the possible preventive role of focused interventions [i.e. psychological therapy or antipsychotic (AP) medication] (Nelson et al., 2016; van der Gaag et al., 2013) as well as the different clinical intake of recent UHR cohorts in comparison with earlier cohorts (Hartmann et al., 2016). However, none of these factors, although all empirically plausible and partly substantiated, is explanatory enough or satisfactory at a conceptual level. A better understanding of the dilution effect is mandatory for the field of early detection/intervention, since it would impact its evidence-basis as well as its strategic societal goals. In this perspective the mere criterial approach to define transition to psychosis has been criticized (van Os & Guloksuz, 2017) and a more radical and widespread aspect (i.e. the classical 'elephant in the room') could have been often overlooked, namely the prescription of antipsychotics (AP) in UHR samples (Raballo, Poletti, & Carpenter, 2019).

In the UHR model, in addition to the criterial transition (based on rating scales), a functional equivalent of transition has been explicitly mentioned as the threshold at which AP treatment would be commenced in common clinical practice (Yung et al., 2003). Albeit apparently subjective and arbitrary, such threshold is based on the real-world, collegial decision making of the treating staff and reflects a global apprehension of the severity of a clinical status requiring AP medication. Clearly, this indicates the end-point of the UHR state and signals 'the threshold for onset of a psychotic episode' (Yung et al., 2005).

Table 1. Synopsis of criterial and functional equivalents of transitions to psychosis in studies reporting exposure to AP at follow-up (censed in Fusar-Poli et al., 2016b)

Study	Assessment instrument	CHR + baseline	Follow-up (months)	Criterial (psychometric) transition (%)[a]	Functional equivalent of transition (%)[b]	Transition spread (functional–criterial transition) (%)[d]	Functional *v.* criterial transition ratio[e]	Note
Woods et al. (2009)	SIPS	259	6, 12, 24, 30	40	37.8	**−2.2**	**0.9**	AP exposure at baseline and follow-up not found in the source article
Lemos-Giraldez et al. (2009)[c]	SIPS	61	6, 12, 24, 36	23	78.7	**+55.7**	**3.4**	48/61 undergo AP after UHR diagnosis (37 AP + CBT; 13 AP) Conversion rate at 3 years: 27% in AP 29% in AP + CBT; 0% in CBT
Nelson et al. (2011)	CAARMS	398	6	18.1	13.6	**−4.5**	**0.8**	5.0% AP at baseline (41/817)
Liu et al. (2011)[c]	SIPS	59	6, 12, 24, 36	35.6	79.7	**+44.1**	**2.2**	AP y/n: 20/1 converters 27/11 non-converters at baseline
Ziermans et al. (2011)	SIPS	65	6, 12, 24	13.0	28.1	**+15.1**	**2.2**	AP 18/72 baseline (25%)
Addington et al. (2012)	SIPS	172	6, 12, 24	20.3	2.9	**−17.4**	**0.14**	Participants were excluded if AP at baseline. AP not used at any later points
Simon et al. (2012)[c]	SIPS/SPI-A	73	12, 24	13.69	15.1	**+1.4**	**1.1**	
Kim et al. (2012)[c]	CAARMS	78	6, 12, 24, 36, ⩾48	17.9	74.4	**+56.5**	**4.15**	
Fusar Poli et al. (2013)[c]	CAARMS	290	6, 12, 24	15.7	23.1	**+7.4**	**1.5**	Not reported if all converters were on AP
Koike et al. (2013)	SIPS	37	6, 12, 24	35.3	46	**+10.7**	**1.3**	AP exposure at baseline and follow-up not found in the source article
Schultze-Lutter et al. (2014)	SIPS/SPI-A/ BSABS	194	6, 12, 24, 36, ⩾48	41.7	21.6	**−20.1**	**0.5**	246 patients at baseline (194 CHR: 37 UHR, 30 BS, 127 UHR + BS). 81 converters at 4 years At baseline 6% AP in non-converters; 53.1% AP in converters
Zhang et al. (2014)[c]	SIPS	89	6, 12, 24	15.73	51.3	**+35.6**	**3.3**	8 non-converters on AP at follow-up
Kotlicka-Antzack et al. (2014)	CAARMS	94	36	18.5	13.8	**−4.7**	**0.74**	AP exposure at baseline and follow-up not found in the source article
Katsura et al. (2014)[c]	CAARMS	106	36	13.2	36.8	**+23.6**	**2.8**	31 UHR on AP at baseline: 22 of them still received AP at least once during follow-up; 17 UHR received AP after baseline; at follow-up: 25 patients on AP, 11 converters 13 non-converters
Spada et al. (2015)[c]	CAARMS	22	6	18.2	45.5	**+27.3**	**2.5**	4 on AP at baseline; 13 UHR and 4 HRneg on AP after baseline
Labad et al. (2015)[c]	CAARMS	39	6, 12	25.6	28.2	**+2.6**	**1.1**	7 on AP at baseline
Bang et al. (2015)[c]	SIPS	60	6, 12, 24	18.3	36.7	**+18.4**	**2.0**	22 UHR on AP at baseline At follow-up 18 non-converters in AP 4 converters in AP

(*Continued*)

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Study	Assessment instrument	CHR + baseline	Follow-up (months)	Criterial (psychometric) transition (%)[a]	Functional equivalent of transition (%)[b]	Transition spread (functional–criterial transition) (%)[d]	Functional *v.* criterial transition ratio[e]	Note
Metzler et al. (2015)	SIPS/SPI-A/CY	44 UHR 28 BS	12	16.6	44.5	**+27.9**	**2.7**	In the sample included at baseline 14 at risk of bipolar disorder; 19% of patients on AP at baseline; 32% at follow-up
Katagiri et al. (2015)[c]	SIPS	41	12	17.01	73.2	**+56.2**	**4.3**	23 non-converters on AP at follow-up

AP, antipsychotics; BS, basic symptoms; CAARMS, Comprehensive Assessment of At Risk Mental States; CBT, cognitive behavioral therapy; CHR, clinical high risk; CT, Criterial transition based on CHR instrument; FT, functional transition based on AP exposure during follow-up; SIPS, Structured Interview for prodromal symptoms; UHR, ultra-high risk.

[a]% of survival rate of transition calculated on the basis of UHR sample at baseline.

[b]% of exposure to AP as reported in online eTable2 in Supplementary content of Fusar-Poli et al. (2016a, 2016b).

[c]Studies detailing the raw numbers of criterial transitions and AP exposure.

[d]Transition spread: % functional transitions minus % of criterial transitions.

[e]Ratio between functional transitions and criterial transitions.

Note: Criterial (psychometric) transition:

Functional equivalent of transition = mental state requiring AP therapy, derived from the reported exposure to AP during the follow-up.

Transition spread = Functional minus Criterial transition, is an index of:

(1) Mismatch between positive symptoms based psychometric assessment and real world clinical severity requiring immediate AP treatment as a collegial decision of the treating staff.

(2) When positive, indicates the amount of undetected psychotic-equivalent mental states.

(3) When negative, indicates the proportion of individuals converting to psychosis not receiving appropriate treatment.

Functional *v.* criterial transition ratio = proportion between individual exposed to AP medication and individuals reaching psychometric criteria for psychosis, is an alternative index of the amount of undetected psychotic-equivalent mental states relative to the psychometric ones.

Just a little bit like Janus Bifrons, conversion to psychosis could have two complementary faces, one looking to escalating positive symptoms (i.e. the criterial psychometric transition), and the other to the complexity of the global clinical trajectory (i.e. the functional equivalent indexed by the therapeutic need of AP medication).

Lost in transition: the glaring evidence of a clinical–conceptual scotoma

The concept of functional transition is crucial considering that AP need is rather frequent in the clinical management of UHR subjects. Of the 33 studies included in a recent meta-analysis addressing psychosis risk stratification (Fusar-Poli et al., 2016b), 24 studies (72.7%) reported exposure to AP during follow-up, yet without justifying it on the basis of worsened clinical severity or considering it a functional equivalent of conversion to psychosis; among these studies, at least seven (above 20%) included in the UHR sample subjects already on AP at the baseline assessment (i.e. in ostensible contradiction with the original UHR definition).

Considering the threshold at which AP medication would be commenced in common clinical practice as a functional equivalent to threshold for onset of psychosis episode, would substantially change the overall transition rates reported in the literature, since basically all the studies merely report criterial (i.e. psychometric) transitions neglecting the functional ones (Table 1). While this mismatch between criterial and functional equivalents of transition may depend on several, context-dependent factors, it is undeniable that its magnitude cannot be further ignored. For example, just considering the 11 studies in which it was possible to clearly extract the absolute number of both criterial transitions and functional transitions, we found that the amount of functional transitions ($n = 350$) is 215% larger than one of the criterial transitions ($n = 163$).

This might be due to the fact that dimensional rating scales, when evaluating transition from UHR to psychosis, mainly focus on positive symptoms. In clinical practice, however, the need for AP medication is established through a global clinical evaluation of the ongoing mental state, including overall clinical severity as consensually perceived by the treating staff. Such global evaluation would typically consider not only the level of positive symptoms but also concurrent disorganized, negative and accessory psychopathology as well as subtler features of role functioning and quality of life. This is further corroborated by the fact that, if we focus only on UHR criteria, BLIPS appear at higher risk than APS, while if we include symptom severity, negative symptoms, affective symptoms and psychosocial functioning, no clear differences emerge (at the baseline as well as at the follow-up) between UHR subgroups (McHugh et al., 2018), indicating that clinically-meaningful features of UHR mental state reside outside the positive dimension and need full consideration together with the risk/benefit ratio with AP medication (Raballo et al., 2019).

Redeeming the elephant in the room and rethinking the transition paradigm

On the basis of this rather disillusioning photograph (i.e. an average AP exposure that is almost the double of the declared conversion rate: about 40% *v.* 22%, see Table 1) we could either hypothesize that UHR subjects are unduly over-exposed to off-label AP (although they do not reach the psychometric threshold for psychosis) or – in line with the original PACE criteria – that

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functional equivalents of transition to psychosis (i.e. a mental state requiring immediate AP medication) are systematically ignored. This widespread clinical and conceptual flaw could be involved in the surface-level phenomenon of dilution effect of criterial transition rate, or – at least – contribute substantially to its magnification. Indeed, when considering both criterial and functional transitions, the magnitude of the overall transition to psychosis almost redoubles and the dilution effect may vary substantially. Even more crucially, mainstream prediction models (typically limited to psychometric transitions and counting UHR undergoing AP treatment as simple non-converters) presumably underestimate natural course transition rates. Therefore, while a re-analysis of available datasets is highly recommendable, a new wave of UHR studies with more transparent and systematic reporting of AP exposure is clearly necessary, with AP continuation without apparent criterial transition being rigorously examined. Finally, the possible underestimation of transition to psychosis in UHR subjects should be considered in the current debate on resource allocation within early detection centers.

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